Inhalation Exposure Waivers for Pesticides

(A guidance document for pesticide registrants)

by Committee Members:

John Whalan, Donald Cooper, Dennis Gibbons, John Rossc, James Sanbornc

Executive Summary

Under the umbrella of the North American Free Trade Agreement (NAFTA), the Technical Pesticide Working Group formed to harmonize the pesticide regulatory processes between the US EPA, Health Canada, and the California Department of Pesticide regulation. Staff from each of these agencies worked together on a variety of issues to reduce the amount of regulatory redundancy. One of the issues was inhalation exposure waivers for pesticides.

Registration of pesticides in the United States and Canada requires inhalation toxicology studies to evaluate the potential for adverse health effects from inhalation if there is significant potential inhalation exposure while handling formulations during mixing, loading, or application. This document seeks to define science-based criteria that may be used to waive studies that assess inhalation exposure when the potential for human exposure during handling or application of a particular pesticide formulation has very low probability of occurrence.

The committee's deliberations involved consideration of physical and chemical properties of the active ingredient, primarily the vapor pressure, particle size of solid formulations, particle size of aerosols, and the potential for friability of solid formulations and the resultant formation of inhalable fines. Each of these factors plays a role in the potential of a pesticide formulation to be inspired and contribute to exposure during handling of pesticides.

Committee Recommendations: Candidates for Inhalation Exposure Waivers

Waivers Based on Volatility

Non-volatile products which are not aerosolized, heated, evaporated, or otherwise made available for inhalation during mixing/loading or application. Non-volatile products are defined as those having vapor pressures <1 x 10-5 kPa (7.5 x 10-5 mm Hg) for indoor uses, and <1 x 10-4 kPa (7.5 x 10-4 mm Hg) for outdoor uses at 20-30oC. Examples of formulations which may be good candidates for waivers based on volatility:

Viscous liquids, waxes, resins, lotions, tree injections, paints, caulks.
Animal dips, shampoos, and pour-ons.
Slow release collars and ear tags.

Waivers Based on Engineering Solutions

Products handled using specific engineering controls that mitigate inhalation exposure.

Closed systems, enclosed cabs. Mitigation must cover the entire mix/load/application process. Example: Soil-applied formulations in boxes that are filled at the distributor and with no contact during use.

Waivers Based on Large Particle Size

of particles

Formulations or application methods that yield a non-inhalable size (99% > 100 micrometers).

Microencapsulated formulations which are not biologically available for inhalation during mixing/loading or application.

Products that are non-inhalable during use due to large particle size. Example: Baits applied by hand or during seed planting, non-inhalable granules placed in or on the soil.

Non-friable granular product formulations.

POSITION PAPER
Issue: Inhalation Exposure Waivers

Item #: H
Description: Guidance for waiving inhalation exposure data for pesticides

Agency Approaches:

U.S. EPA:

On December 8, 1991, the Health Effects Division (HED) issued a "Policy on Acute Inhalation Toxicity Data Waivers." This policy describes the types of products that pose little or no inhalation hazard, and are therefore candidates for waivers from inhalation toxicity studies. All products are considered on a case-by-case basis, and the Agency reserves the right to request studies. Reasoning that products that do not need toxicity studies also do not need exposure studies, HED's guidance was adopted by NAFTA as a criteria for waiving inhalation exposure studies. The NAFTA project provides an opportunity to establish a policy which is practical and in harmony with other regulatory agencies.

Health Canada:

The current PMRA position on waivers for toxicity and inhalation exposure studies is simply: "PMRA considers requests for waivers of inhalation toxicology and inhalation exposure studies on a case-by-case basis."

DPR:

DPR considers waivers for toxicity and inhalation exposure studies on a case by case basis also, but has a guidance document (Memorandum from Rutz to Wang, 1989).

Harmonization Status:

All participants agree with the content of this document.

Recommendation for Continued Progress:

In the process of investigating exposure waiver issues the workgroup also researched the following issues. The workgroup recommends completion of the following:

The applicability for inhalation exposure waivers for re-entry scenarios.
The potential for inhalation toxicology study waivers based on similar criteria.
Decision flow diagram for mitigation of pesticide respiratory hazards.
Use of PHED exposure data base to assess the relative contribution of inhalation exposure.

Inhalation Exposure Waivers for Pesticides

(A guidance document for pesticide registrants)

by Committee Members:

John Whalan, Donald Cooper, Dennis Gibbons, John Rossc, James Sanbornc

CONTENTS

1.0 Introduction

Under the umbrella of the North American Free Trade Agreement (NAFTA), the Technical Pesticide Working Group formed to harmonize the pesticide regulatory processes between the US EPA, Health Canada and the California Department of Pesticide regulation. Staff from each of these agencies worked together on a variety of issues to reduce the amount of regulatory redundancy. One of the issues was inhalation exposure waivers for pesticides.

This document seeks to define science-based criteria that may be used to waive studies that assess inhalation exposure when the potential for human exposure during mixing, loading, and application of a particular pesticide formulation has very low probability of occurrence.

For most active ingredients, granting a waiver for an inhalation exposure study will not occur frequently because the exposure during handling or application cannot be considered to be insignificant. However, for some formulations such as those on granules that are placed in or on the soil that do not contain inspirable particles, baits applied by hand or during seed planting, or soil-applied formulations in boxes that are filled at the distributor and with no contact during use, the potential for inhalation exposure may be minimal. For these types of formulations, the requirement for an inhalation exposure study may be waived.

The document that follows describes the results of deliberations between staff from the United State's Environmental Protection Agency (US EPA), the California Department of Pesticide Regulation (DPR) and Health Canada (HC) to develop criteria that can be used to waive inhalation exposure studies for pesticides. These discussions involved consideration of physical and chemical properties of the active ingredient, (primarily the vapor pressure), particle size of solid formulations, particle size of aerosols, and the potential for friability of solid formulations and the resultant formation of fines. Each of these factors plays a role in the potential of a pesticide formulation to be inspired and contribute to exposure during handling of pesticides.

The primary intent of this report is to convey in a clear, concise, and reasonable fashion some guidance that can be used by regulators and registrants as a basis for a waiver of inhalation data. In addition this document contains references that should find utility for those involved in the regulatory process either as a pesticide registrant or a member of government.

Pesticide products which do not pose significant inhalation potential are candidates for study waivers. Nevertheless, the US EPA, Health Canada, and Cal/DPR, reserve the right to request studies on a case-by-case basis.

The following provides criteria and examples for pesticide formulations for which inhalation exposure studies can be waived. It must be remembered that handling of pesticide products may involve two operations, namely the mix/load and the application.

All phases of mixing/loading and application must be considered although application frequently provides more opportunity for inhalation exposure than mix/load. An air blast application with no respiratory protection from either a cab or a respirator scenario will generally present greater exposure than a ground application with granular formulations applied at planting in tandem with a grain drill. Because a variety of exposure potentials exist, regulatory agencies reserve the prerogative to consider each formulation on a case-by-case basis to ensure protection of the pesticide formulation handler.

2.0 Criteria for Inhalation Exposure Waivers

2.1 Recommendation Based on Volatility

Non-volatile products which are not readily aerosolized, and which are not heated, evaporated, or diluted to an inhalable state during application. Non-volatile products are defined as those having vapor pressures less than 1 x 10-5 kPa (7.5 x 10-5 mm Hg) for indoor uses, and less than 1 x 10-4 kPa (7.5 x 10-4 mm Hg) for outdoor uses at 20-30oC.

Examples of formulations which may be good candidates for waivers based on volatility:

Viscous liquids, waxes, resins, lotions, tree injections, paints, caulks, etc.

Animal dips, shampoos, and pour-ons.

Slow release collars and ear tags.

2.2 Waivers Based on Engineering Solutions

Products handled using specific engineering controls that mitigate inhalation exposure.

Examples of engineering controls which may allow a product to be a good candidate for waiver:

Closed Systems. For formulations used in closed systems for the entire mix/load/application process.

Enclosed cabs. For products applied using enclosed cabs providing respiratory protection and when any other associated mixing/loading inhalation hazard is also mitigated.

2.3 Waivers Based on Large Particle Size

Product formulations or application methods that yield a non-inhalable particle size (99 percent of particles greater than 100 micrometers in aerodynamic diameter).

Examples of formulations which may be good candidates for waivers:

Microencapsulated formulations which are not biologically available for inhalation during mixing/loading or application.

Granular products placed in or on the soil, baits applied by hand or during seed planting.

In cases where solids are being proposed as candidates for inhalation exposure waivers, it will be further required that

the solid be proven to be non-friable as defined by the ASTM Attrition Workgroup.

3.0 Rationale for Inhalation Exposure Waivers Criteria

3.1 Rationale for Volatility as a Determinant for Inhalation Exposure Waiver

In order to validate cut-off vapor pressures below which exposure could be assumed to be non-significant, exposure data for a number of theoretical scenarios was generated using conservative methods (*i.e.*, saturated vapor concentration which greatly overestimates actual airborne concentrations found in practice). In order to achieve this goal, several tables were developed with each table providing the foundation for the subsequent one. Some of the entries in the tables have many figures to the right of the decimal point. This was necessary as some of the entries in the tables ranged up to 100,000-fold (*e.g.,* Table 3 where the range is 105 fold). If the values in some of the tables were rounded off to two significant figures, the smaller values are then zeros and the information in these cells is lost for comparison purposes.

Conversion of air concentrations at saturation from ppm to ug/m3

The first table describes the air concentration of a pesticide in mg/m3 at saturation and its dependence on two variables, molecular weight (100, 250, 500) and vapor pressure (10-5 mm Hg). The two formulae used for calculation of the entries in Table 1 are shown below:

Saturation concentration (ppm) = Vapor Pressure (mm Hg)/760 mm x 106

(Typically determined for room temperature from vapor pressures at 20oC)

Conversion to mass/volume (mg/m3) = ppm x molecular weight (MW)/24.45

(at 760 mm Hg and 25oC)

Table 1. The dependency of air concentration on molecular weight and vapor pressure.

	Molecular weight		
	100	250	500

VP (mm)	PPM	Air concentration (mg/m3)		
1	1315.79	5381.55	13,453.8	26,907.76
0.1	131.58	53816.	1345.39	2690.78
0.01	13.16	53.82	134.54	269.08
0.001	1.32	5.38	13.45	26.91
0.0001	0.13	0.54	1.35	2.69
0.00001	0.01	0.05	0.13	0.27

The values in the PPM column were obtained from the first equation. The values in the next three columns with units of mg/m3 are obtained from the ppm values by the second equation by first multiplying the air concentration in ppm by the molecular weight of the pesticide and then dividing by 24.45. For example, if the vapor pressure of a hypothetical pesticide is 10-4 mm (shaded), the maximum air concentration might approach 0.13 ppm (small arrow). If this pesticide has a molecular weight of 250 (shaded), then the air concentration might approach 1.35 mg/m3 (large arrow). These air levels will not be found in most work situations, because local building codes will require a minimum number of air changes per hour indoors and outdoors, air changes are virtually infinite. Even in a "tight" house built to reduce energy consumption, air turnovers usually exceed 2/hr.

Estimation of absorbed daily dosage (ADD) from air levels in Table 1

The data in Table 2 provide information on the absorbed daily dosage from exposure to the air concentrations derived in Table 1. To obtain the absorbed daily dosages in this table, it is assumed that the exposure duration is 8 hours, the respiratory uptake of a vapor is 50% (Raabe, 1989), the body weight is 70 kg, and the respiratory rate is 1 m3/hr.

Table 2: Absorbed daily dosages (ADD) at saturated air concentrations

	Molecular weight		
	100	250	500
VP (mm)	Absorbed Daily Dosage (mg/kg)		
1	307.517	768.793	1537.586
0.1	30.752	76.879	153.759

0.01	3.075	7.688	15.376
0.001	0.308	0.769	1.538
0.0001	0.031	0.077	0.154
0.00001	0.003	0.008	0.015

To continue the estimation of exposure of a pesticide that has a vapor pressure of 10-4 mm and a molecular weight of 250, the ADD value in the cell with the arrow (0.077 mg/kg) is calculated as follows:

$$\frac{\text{Air Concentration x Respiratory Rate x Absorption x Exposure Duration}}{\text{Body Weight}}$$

= 1.35 mg/m3 x 1 m3/hr x 0.5 x 8 hr/70 kg = 0.077 mg/kg/day

Using a similar strategy, the rest of the values in this table were calculated. The ADD from inhalation, 77 µg/kg, must be placed in some perspective. In most mixing/loading/application pesticide exposure scenarios, the contribution of inhalation to the total exposure ranges from 1-3%, according to existing data bases. (Wolfe, 1976, PHED). For this example of a pesticide that has a vapor pressure of 10-4 mm and a molecular weight of 250, the ADD by other routes (assume remainder dermal) may be ~33-100 times the inhalation value or 2.5-7.7 mg/kg (33-100 x 0.077mg). Conversion of this range of dermal doses in units of mg/kg into mg/person first dividing by a hypothetical 0.25 for a penetration factor gives a dermal dose of 10-31 mg/kg. Multiplying by 70 will provide a dermal dose range of 700-2170 mg/person. These calculations do not include any consideration of the amount of pounds handled. The estimates are solely based on the vapor pressure of the hypothetical pesticide and the molecular weight. The magnitude of these exposures calculated strictly on the basis of vapor pressure and molecular weight can be compared with PHED-derived values for an air blast application with an open cab (no cab) where the exposures (inhalation) are high. For an open cab, the inhalation exposure factor for airblast application is 4.5 µg/lb handled (BASET, 1996). If it is assumed that 100 lbs of active ingredient are applied, then the exposure would be 450 µg/person. The Absorbed Dosage via inhalation assuming 50% for gas phase uptake and a 70 kg body weight would be 3.2 µg/kg or slightly less than 25-fold lower than the dose estimate only based on molecular weight and physical properties.

Estimation of Lifetime Average Daily Dosage (LADD) from ADD values in Table 2

To estimate a lifetime average daily dosage (LADD) data from the

ADD values in Table 2, it is assumed that the exposure duration and length of lifetime are 40 and 75 years, respectively. These LADD data are summarized in Table 3.

Table 3: Lifetime Average Daily Dosage (LADD) from Table 2 ADD values

	Molecular weight		
	100	250	500
VP (mm)	ADD (mg/kg/day)		
1	89.8681	224.6701	449.3403
0.1	8.9868	22.4670	44.9340
0.01	0.8987	2.2467	4.4934
0.001	0.0899	0.2247	0.4493
0.0001	0.0090	0.0225	0.0449
0.00001	0.0009	0.0022	0.0045

To illustrate the method used to calculate the values in Table 3, the LADD for a hypothetical pesticide with a vapor pressure of 10-4 mm (shaded cell) and a molecular weight of 250 (shaded cell), the equation shown below was utilized to derived the estimate in the cell with the arrow:
LADD (mg/kg/day) = ADD (mg/kg/day) x exposure days/yr x exposure duration (years)/life (years)
LADD (mg/kg/day) = 0.077 mg/kg/day x 200 days/365 days/year x 40 years/75 years = 0.0225

Estimation Q1* values to obtain a lifetime risk of 10-5 from LADD estimates

If it is assumed that the data in Table 3 represents exposure to a pesticide that is a carcinogen, then it is useful to calculate a carcinogenic potency (Q1*) estimate for each LADD value that would provide a lifetime risk of 10-5 or less.

Table 4. Q1* values for LADD values in Table 3 that provide a risk of 10-5

	Molecular weight		
	100	250	500

VP (mm)	Q1* (mg/kg/day)-1		
1	1.1E-07	4.5E-08	2.2E-08
0.1	1.1E-06	4.5E-07	2.2E-07
0.01	1.1E-05	4.5E-06	2.2E-06
0.001	0.00011	4.5E-05	2.2E-05
0.0001	0.0011	0.00045	0.00022
0.00001	0.011	0.0045	0.0022

In a continuation of an estimate for the hypothetical pesticide that has a vapor pressure of 10-4 mm and a molecular weight of 250, the Q1* value that would provide a 10-5 risk is 0.00045 (mg/kg/day)-1 (large arrow). This value was calculated using the following equation:

Q1* = 10-5/LADD (mg/kg/day) = 10-5/0.0247 (mg/kg/day)-1 = 0.00045

This value is much lower than the median of cancer potency values assembled by the U.S. EPA (IRIS) which ranges between 0.01-0.09/(mg/kg/day) for values.

Estimation of Margin of Safety (MOS) or Margin of Exposure (MOE) values from LADD Data in Table 3 for a chronic toxicology endpoint.

The LADD values in Table 3 are the basis for calculations of MOE values in Table 5. If the NOEL for these calculations is assumed to be 1 mg/kg and the MOE is required to be equal or greater than 100, then the chronic human exposures must be equal or below 0.01 mg/kg.

Table 5. Margin of Exposure (MOE) estimates from LADD values in Table 3 for a chronic toxicology endpoint

	Molecular weight		
	100	250	500
VP (mm)	MOE		
1	0.01	0.00	0.00
0.1	0.11	0.04	0.02
0.01	1.1	0.4	0.2
0.001	11.1	4.5	2.2
0.0001	111.3	44.5	22.3
0.00001	1112.7	445.1	222.5

Examination of the data in Table 5, indicates that only 4 values (shaded area below line in table above) have a margin of exposure that is > 100. Again, to illustrate the calculations for a hypothetical pesticide that has a vapor pressure of 10-4 mm and a molecular weight of 250, the equation below was used to obtain the result in the cell with the arrow.
MOE = Animal NOEL/LADD = 1 mg/kg/ 0.022 mg/kg = 44.5

MOE values for animal NOEL values that are either greater or lower than 1 mg/kg

If the animal NOEL were either greater or less than 1 mg/kg, then the MOE would be different for the example above. If the NOEL were 0.1 mg/kg, then the MOE would be 4.5. On the other hand if the NOEL were 10 mg/kg, then the MOE would be 445.

3.2 Rationale Based on Engineering Solutions

Engineering controls can be used to prevent or minimize inhalation exposure. If exposure is controlled by specifying some engineering control, a pesticide product may be a candidate for a waiver. A product might be handled entirely within a closed system and never enter the work place environment. An example might be a seed treating procedure where the pesticide product is removed from the container through a closed transfer system, transferred into an enclosed and ventilated seed treater, and subsequently bagged with equipment designed to mitigate any dust or vapor exposure. Another product might carry instruction to apply with application equipment equipped with a respiratory protective enclosed cab.

3.3 Rationale Based on Large Particle Size

A product might be formulated as a microencapsulated product which eliminates any possible inhalation concern provided the shell remains intact and/or the microcapsules are too large to be inhaled.

Even if purposely aerosolized (sprayed, misted) in the work place, a product might be a candidate for waiver if the specified application equipment does not produce airborne particulate matter of significant inhalation size and concentration.

Regarding particulate matter, particles up to 100 micrometers are considered to be inhalable (ACGIH, 1985; Vincent, 1995).

Consequently, candidates for waivers based on particle size during use, must be applied without production of any significant amount of particles in sizes below about 100 micrometers aerodynamic diameter

Regarding concentration, since the volume and consequent mass of a particle vary as a cube of the radius, a waiver might be appropriate if application of the product precludes generation of any significant airborne inhalable concentration of particles. For example, if 99 percent of a spray aerosol is composed of particles greater than 100 micrometers and the sizes do not change significantly while present in the workplace airborne environment before reaching their target, the concentration in the remaining 1 percent might be considered to be insignificant. Alternatively, a product label might specify application equipment known to allow application while maintaining workplace aerosol concentrations below an acceptable level (for example, a Permissible Exposure Limit or other recognized exposure value) for the specific product.

4.0 Granule Friability and the Potential for Inhalation Exposure: Methodology for Determination of Friability (Attrition).

The following is a draft protocol for the assessment of the friability of granular formulations. The finalization of these guidelines will not occur until early in 1998. The American Society of Testing Materials (ASTM) Attrition Workgroup met October 13-17, 1997 to discuss a protocol for assessing granular attrition. The intent of this project is to standardize a rationale for assessing whether a granular product poses an inhalation hazard from the production of inspirable particles. Those products that do not have an attrition problem are candidates for waivers from further toxicity and exposure studies. 140

The ASTM Workgroup proposes the following steps:

1. Dry screen test. The granular product is placed on a ~~125~~ 106 micrometer screen (~~270~~ mesh) and agitated by shaking or ~~hammering~~ tapping. If >1% of the product passes through the screen, toxicity and/or exposure studies are required. If less than 1% of the product passes through the screen, proceed to step 2 to assess attrition.
2. CIPAC (Collaborative International Pesticide Analytical Council) MT-178 Friability Standard: Fifty grams of granules and 50 grams of glass beads are slowly tumbled for an hour, then poured over a 106 ~~125~~ micrometer screen as described in step 1. If >1% of the product passes through the screen, attrition is a potential hazard, so toxicity and/or exposure studies are required. If less than 1% of the product passes through the screen, the product does not pose an attrition hazard.

This approach is inexpensive and easy to perform at any laboratory. It

uses the internationally accepted CIPAC protocol. The ASTM Workgroup will quantify screening methods using alpine sieves, air puffs, sonic sifters, and laser sizing. The CIPAC protocol should work for about 90% of the granular pesticide products.

Commentary on Draft Friability Guidelines for granular formulations Protocol

The simplicity of the foregoing guidelines suggests that they can be implemented by the registrants. It is important to recognize that there will need to be some calibration of these results with those obtained from actual formulations that move in the channels of trade.

In an ideal situation, the data (particle size distribution) from this standardized protocol should be comparable to that obtained from containers of formulations that are transported from the formulation and packaging facility to the use site where exposure may occur. Perhaps data already exist from CIPAC that show this comparison.

Even though a formulation passes the CIPAC protocol, a waiver may be denied if there is a possibility that a small percentage of extremely toxic (Category 1) particles may be inhaled. A mitigating factor if an exposure study were conducted would be the respiratory protection (either PPE or engineering controls *i.e.,* closed loading systems and closed cabs) required by the governmental regulations for pesticides designated as Category I. While levels of exposure external to either PPE or engineering controls might reach levels of concern, it is unlikely inside these devices that occupational exposure air concentrations would exist (assuming IH PPE or engineering protection factors) that would still be of concern.

References

American Conference of Governmental Industrial Hygienists: Particle Size-Selective Sampling in the Workplace. ACGIH, Cincinnati, OH (1985).

PHED Surrogate Exposure Guide, Best Available Surrogate Exposure Tables, (BASET), U.S. EPA, 1996.

Raabe, O.G. (1989) Retention and metabolism of toxics: Inhalation Uptake of xenobiotics by people CARB Contract No. A5-155-3.

Vincent, J.H.: (1995) Aerosol Science for Industrial Hygienists. Elsevier Science Limited, Oxford.

Wolfe, H.R., (1976) Field exposure to airborne pesticides. In Air Pollution from Pesticides and Agricultural Processes, Ed. R.E. Lee pp 137-161.